

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: AOKI et al.) Examiner: A. Gupta
) (parent app.)
Serial Number: Pending)
) Art Unit: 1653
Filed: Herein) (parent app.)
)
For: METHOD FOR TREATING MUSCLE SPASM)
WITH BOTULINUM TOXIN TYPE B) Irvine, California

Assistant Commissioner of Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

I. Introduction

This application is a divisional of pending application serial number 09/490,756, filed January 24, 2000, which is a divisional of application serial number 08/627,118, filed April 3, 1996, which is a continuation of application serial number 08/173,966, filed December 28, 1993, now abandoned.

II. Amendments to the Specification

The title of the application has been replaced by a title more descriptive of the claimed subject matter and a cross reference to the parent patent applications has been added to page one of the specification.

For "CO" 25040000

III. New Claims 21-31

Original claims 1-20 are cancelled and new claims 21-31 are added to this application by this preliminary amendment. All of the new claims 21-31 are supported by the original specification as set forth below:

Claim 21 is directed to a method for treating a muscle spasm using botulinum toxin type B, and claim 21 is supported by at least Examples 1, 2, 3, 4, 6, 7, 8, 9, 9 and 10 of the original specification. The Examples set forth use of botulinum toxin type B to treat broad and diverse muscle spasms. Examples 6, 7, 8, 9 and 9 (second example 9) are entitled "The Use of Botulinum Toxin Types A-G in the Treatment of Muscle Spasms...".

The Examples set forth examples of use of botulinum toxin type B toxin to treat tardive dyskinesia muscle spasms (Example 1), spasmodic torticollis muscle spasms (Example 2(a)), essential tremor muscle spasms (Example 3), spasmodic dysphonia muscle spasms (Example 4), smooth sphincter muscle spasms (Example 6), Temporal Mandibular Joint muscle spasms (Example 7), sports injury muscle spasms (Example 8), smooth muscle gastrointestinal muscle spasm (Example 9), muscle spasms secondary to trauma (Example 9), and throat muscle spasms (Example 10).

Claim 22 is supported by at least page 7, lines 11-15 of the specification.

Claim 23 is supported by at least Examples 6, 7, 8 and 9 on pages 17-18 of the specification.

Claim 24 is supported by at least page 8, lines 24-26 of the specification and Example 2(a) on page 11, lines 10-15 of the specification.

Claim 25 is supported by at least page 1, line 24 of the specification.

Claim 26 is supported by at least page 1, line 23 of the specification.

Claim 27 incorporates the limitations of claims 21, 22 and 23.

Claim 28 is supported by at least page 1, line 24 of the specification.

Claim 29 is supported by at least page 1, line 23 of the specification.

Claim 30 incorporates the limitations of 21, 22, 23 and 25.

Claim 31 incorporates the limitations of claims 21, 22 , 23 and 26.

IV. Claims 21-31 are in Condition for Allowance

Enclosed is a copy of the February 8, 2001 declaration of Mitchell Brin, which declaration was submitted in co-pending application serial number 09/490,756 with applicants response dated February 16, 2001 in co-pending application serial number 09/490,756.

Paragraph 6 of the Brin declaration states: "As of the April 25, 1991 date of the Jankovic reference it was completely unknown as to whether or not botulinum toxin type B would have any therapeutic efficacy in humans. Indeed, as far as I am aware, the first reported use of type B botulinum toxin in humans did not occur until 1995."

Additionally, paragraph 8 of the Brin declaration states: "In my opinion, prior to December 28, 1993, it would have been foolhardy and dangerous to use botulinum toxin type B to treat patients with dystonia, such as cervical dystonia,

in light of the complete lack of clinical experience with the type B toxin as of that date."

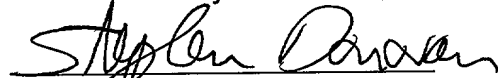
The Brin declaration is submitted herein as evidence that the claims in this application are in condition for allowance. In other words, since there had been no use of botulinum toxin type B to treat any disease condition prior to the effective filing date of the present application (December 23, 1993) and based upon the additional evidence presented by the Brin declaration, the present claims 21-31 being directed to use of a botulinum toxin type B to treat a muscle spasm are free of the art and in condition for allowance.

V. Conclusion

Examination and allowance of claims 21-31 is requested.

Date: July 11, 2001

Respectfully Submitted,



Stephen Donovan

Registration Number 33,433

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CERTIFICATE OF EXPRESS MAIL UNDER 37 C.F.R. § 1.10

I hereby certify that the Transmittal Letter, the divisional patent application, preliminary amendment, and the documents referred to as enclosed therein are being deposited with the United States Postal Service on this date July 11, 2001

in an envelope as "Express Mail Post Office to Addressee" Mailing Label number
EL385557492US addressed to Box Patent Application, Assistant Commissioner
for Patents, Washington, D.C. 20231

Susan Bartholomew

Name of person mailing paper



Signature of person mailing paper

Date: July 11, 2001

Variable	Mean	SD	Min	Max
Age	38.5	12.5	20	65
Gender	0.5	0.5	0	1
Marital status	0.5	0.5	0	1
Education	12.5	2.5	9	16
Income	15.5	10.5	5	35
Occupation	1.5	1.5	0	3
Health status	1.5	1.5	0	3
Stress level	2.5	1.5	0	4
Life satisfaction	3.5	1.5	1	5
Depression	1.5	1.5	0	3
Anxiety	1.5	1.5	0	3
Loneliness	1.5	1.5	0	3
Self-esteem	3.5	1.5	1	5
Resilience	3.5	1.5	1	5
Optimism	3.5	1.5	1	5
Gratitude	3.5	1.5	1	5
Forgiveness	3.5	1.5	1	5
Compassion	3.5	1.5	1	5
Kindness	3.5	1.5	1	5
Patience	3.5	1.5	1	5
Humility	3.5	1.5	1	5
Modesty	3.5	1.5	1	5
Generosity	3.5	1.5	1	5
Generous	3.5	1.5	1	5
Kind	3.5	1.5	1	5
Compassionate	3.5	1.5	1	5
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Generous	3.5	1.5	1	5
Kind	3.5	1.5	1	5
Compassionate	3.5	1.5	1	5
Forgiving	3.5	1.5	1	5
Kindness	3.5	1.5	1	5
Patience	3.5	1.5	1	5
Humility	3.5	1.5	1	5
Modesty	3.5	1.5	1	5
Generosity	3.5	1.5	1	

METHOD FOR TREATING MUSCLE SPASM WITH BOTULINUM TOXIN TYPE B

CROSS REFERENCE

This application is a divisional of application serial number 09/490,756, filed January 24, 2000, which is a divisional of serial number 08/627,118, filed April 3, 1996, which is a continuation serial number 08/173,996, filed December 28, 1993, now abandoned.

FIELD OF THE INVENTION

The present invention provides novel methods for treating various disorders and conditions, with Botulinum toxins. Importantly, the present invention provides methods useful in relieving pain related to muscle activity or contracture and therefore is of advantage in the treatment of, for example, muscle spasm such as Temporomandibular Joint Disease, low back pain, myofascial pain, pain related to spasticity and dystonia, as well as sports injuries, and pain related to contractures in arthritis.

BACKGROUND OF THE INVENTION

Heretofore, Botulinum toxins, in particular Botulinum toxin type A, has been used in the treatment of a number of neuromuscular disorders and conditions involving muscular spasm; for example, strabismus, blepharospasm, spasmodic torticollis (cervical dystonia), oromandibular dystonia and spasmodic dysphonia (laryngeal dystonia). The toxin binds rapidly and strongly to presynaptic cholinergic nerve terminals and inhibits the exocytosis of acetylcholine by decreasing the frequency of acetylcholine release. This results in local paralysis and hence relaxation of the muscles afflicted by spasm.

For one example of treating neuromuscular disorders, see U.S. Patent No. 5,053,005 to Borodic, which suggests treating curvature of the juvenile

**THE FOLLOWING PAGES SHOWS A MARKED UP VERSION OF PAGE 1 OF
THE SPECIFICATION**

000007-0740
TOP20250400

METHOD FOR TREATING MUSCLE SPASM WITH USE OF BOTULINUM
TOXIN TYPE B FOR TREATING VARIOUS DISORDERS AND CONDITIONS
AND ASSOCIATED PAIN

CROSS REFERENCE

This application is divisional of application serial number 09/490,756, filed
January 24, 2000, which is a divisional of serial number 08/627,118, filed April 3,
1996, which is a continuation of serial number 08/173,996, filed December 28,
1993, now abandoned.

FIELD OF THE INVENTION

The present invention provides novel methods for treating various disorders and conditions, with Botulinum toxins. Importantly, the present invention provides methods useful in relieving pain related to muscle activity or contracture and therefore is of advantage in the treatment of, for example, muscle spasm such as Temporomandibular Joint Disease, low back pain, myofascial pain, pain related to spasticity and dystonia, as well as sports injuries, and pain related to contractures in arthritis.

BACKGROUND OF THE INVENTION

Heretofore, Botulinum toxins, in particular Botulinum toxin type A, has been used in the treatment of a number of neuromuscular disorders and conditions involving muscular spasm; for example, strabismus, blepharospasm, spasmodic torticollis (cervical dystonia), oromandibular dystonia and spasmodic dysphonia (laryngeal dystonia). The toxin binds rapidly and strongly to presynaptic cholinergic nerve terminals and inhibits the exocytosis of acetylcholine by decreasing the frequency of acetylcholine release. This results in local paralysis and hence relaxation of the muscles afflicted by spasm.

For one example of treating neuromuscular disorders, see U.S. Patent No. 5,053,005 to Borodic, which suggests treating curvature of the juvenile

**PLEASE REPLACE THE CLAIMS BY THE
FOLLOWING UNMARKED VERSION OF THE CLAIMS**

21. A method for treating a muscle spasm, the method comprising the step of administration of a therapeutically effective amount of a botulinum toxin type B to treat a muscle spasm.
22. The method of claim 21, wherein the botulinum toxin type B is administered by intramuscular injection or by subcutaneous injection.
23. The method of claim 21, wherein the administration of the botulinum toxin type B results in an alleviation of the muscle spasm within 1 day to about 7 days.
24. The method of claim 21, wherein the patient is administered at least 1,000 units of the botulinum toxin type B.
25. The method of claim 21, wherein the muscle spasm is blepharospasm.
26. The method of claim 21, wherein the muscle spasm is a symptom of strabismus.
27. A method for treating a muscle spasm in a human patient, the method comprising the step of administering to a human patient an effective amount of botulinum toxin type B to treat a muscle spasm, wherein the botulinum toxin type B is administered by intramuscular injection or by subcutaneous injection, the

the administration of the botulinum toxin type B resulting in alleviation of the muscle spasm within 1 day to about 7 days.

28. The method of claim 27, wherein the muscle spasm is blepharospasm.

29. The method of claim 27, wherein the muscle spasm is a symptom of strabismus.

30. A method for treating a blepharospasm, the method comprising the step of administering to a human patient a therapeutically effective amount of botulinum toxin type B to treat blepharospasm, wherein the botulinum toxin type B is administered by intramuscular injection or by subcutaneous injection, and the administration of the botulinum toxin type B results in alleviation of the blepharospasm within 1 day to about 7 days.

31. A method for treating a strabismus, the method comprising the step of administering to a human patient a therapeutically effective amount of botulinum toxin type B to treat strabismus, wherein the botulinum toxin type B is administered by intramuscular injection or by subcutaneous injection, and the administration of the botulinum toxin type B results in alleviation of a muscle spasm symptom of the strabismus within 1 day to about 7 days.

MARKED UP VERSION OF THE CLAIMS

Cancel claims 1-20.

Please add the following new claims:

21. A method for treating a muscle spasm, the method comprising the step of administration of a therapeutically effective amount of a botulinum toxin type B to treat a muscle spasm.

22. The method of claim 21, wherein the botulinum toxin type B is administered by intramuscular injection or by subcutaneous injection.

23. The method of claim 21, wherein the administration of the botulinum toxin type B results in an alleviation of the muscle spasm within 1 day to about 7 days.

24. The method of claim 21, wherein the patient is administered at least 1,000 units of the botulinum toxin type B.

25. The method of claim 21, wherein the muscle spasm is blepharospasm.

26. The method of claim 21, wherein the muscle spasm is a symptom of strabismus.

27. A method for treating a muscle spasm in a human patient, the method comprising the step of administering to a human patient an effective amount of botulinum toxin type B to treat a muscle spasm, wherein the botulinum toxin type B is administered by intramuscular injection or by subcutaneous injection , the administration of the botulinum toxin type B resulting in alleviation of the muscle spasm within 1 day to about 7 days.

28. The method of claim 27, wherein the muscle spasm is blepharospasm.

29. The method of claim 27, wherein the muscle spasm is a symptom of strabismus.

30. A method for treating a blepharospasm, the method comprising the step of administering to a human patient a therapeutically effective amount of botulinum toxin type B to treat blepharospasm, wherein the botulinum toxin type B is administered by intramuscular injection or by subcutaneous injection, and the administration of the botulinum toxin type B results in alleviation of the blepharospasm within 1 day to about 7 days.

31. A method for treating a strabismus, the method comprising the step of administering to a human patient a therapeutically effective amount of botulinum toxin type B to treat strabismus, wherein the botulinum toxin type B is administered by intramuscular injection or by subcutaneous injection, and the administration of the botulinum toxin type B results in alleviation of a muscle spasm symptom of the strabismus within 1 day to about 7 days.